Scientific Evaluation of Chloroform

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Topics

- Developmental toxicity
- Male reproductive toxicity
- Female reproductive toxicity

"… although epidemiological studies of this type are useful in evaluating whether chlorinated drinking water can increase the risk of adverse reproductive effects in exposed populations, ***the studies are not adequate to establish a causal link between ingestion of chloroform and the occurrence of adverse reproductive effects*** in humans, because chlorinated drinking water contains many different potentially toxic disinfection byproducts."

--US EPA (2001) [emphasis added]

Developmental Toxicity: Epidemiological Studies

- No causal link established
- All but one are studies of drinking water and THMs (not chloroform alone)
- One occupational study of laboratory workers
- Association sometimes seen for THMs, but no or weaker association with chloroform
- Limitations (e.g., no dose-response, possible exposure misclassification)

Developmental Toxicity: Overview of Animal Studies

- No developmental effects seen in the absence of significant maternal toxicity
- When maternal toxicity was excessive:
  - decreased fetal weight and/or viability was observed
- When maternal toxicity was not excessive:
  - developmental effects were inconsistent among studies
  - maternal toxicity remained the most plausible explanation for effects
- Some studies: not scientifically valid testing

"… [developmental effects] occur only at the same or higher doses as those which cause effects on the dam, suggesting that most of the effects are secondary to maternal toxicity. No studies were located that demonstrate that the fetus is more sensitive to chloroform toxicity than the mother. This is supported by findings that the enzyme responsible for chloroform metabolism (CYP2E1) is low or absent in the fetus."

-- US EPA (2001)

Chloroform Inhalation Studies

Conc, ppm	Maternal Toxicity	Developmental Toxicity
300	Excessive	⇓ viability & FBW
100	⇓ wt gain & food	⇑ fetal anomalies
30	⇓ wt gain & food	⇑ delayed ossification
300	⇓ wt gain & food	⇓ viability & FBW
100	⇓ wt gain & food	No effect
30	⇓ wt gain & food	No effect
30	⇓ wt gain & food	⇓ FBW
10	⇓ wt gain & food	No effect
3	⇓ food (1st wk)	No effect
100	⇓ wt gain; ⇑ liver	⇓ viability and FBW

Role of Maternal Toxicity in Schwetz et al. (1974)

- “Starved” control showed an effect on fetal weight, not viability
- Not a pair-fed control (“starved” ate 4 times more than the high dose group)
- No measurement of water consumption
- Did not control for alternative causative factors
- Maternal toxicity is most likely explanation

Chloroform Oral Studies

Dose mg/kg-d	Maternal Toxicity	Developmental Toxicity
50	Excessive	⇓ FBW
35	Anorexia, diarrhea	No effect
20	Anorexia, diarrhea	⇓ FBW (?)
126	⇓ wt gain & food	⇓ FBW
50	⇓ wt gain	No effect
20	No effect	No effect
400	⇓ wt gain; ⇑ liver; hemat	⇓ FBW; ⇑ sternebral var
200	⇓ wt gain; ⇑ liver; hemat	No effect
100	⇓ wt gain; ⇑ liver; hemat	No effect

Developmental Toxicity: Other Studies

- Neurobehavioral study in mice with both prenatal and postnatal exposure
- HID: “chloroform showed no overall tendency to retard neurobehavioral development of mouse pups.”
- *In vitro* assays are of limited value for human hazard identification and provide no direct evidence of developmental toxicity

Male and Female Reproductive Toxicity

- Epidemiological studies provide no consistent evidence
- Negative NTP continuous breeding study
- Negative 90-day rat and 7.5-yr dog studies
- Developmental toxicity studies suggest female reproductive toxicity only in the presence of maternal toxicity
- Inadequate mouse sperm morphology study

Mouse Sperm Morphology (Land et al., 1979)

- Inadequately reported (abstract only)
- >20% male mortality at 0.08% chloroform
- No dose-response for abnormal morphology
- No details of statistical analysis
- Re-reported in 1981 with more exposed mice
- Inconsistent with the NTP study results

Conclusions

- Epi data, at most, suggest an inconsistent association, not a causal link
- The association is generally stronger for THMs than for chloroform
- Effects seen in animal studies are easily explained by maternal toxicity
- Chloroform has not been “clearly shown to cause” reproductive toxicity